II. REMARKS

Reconsideration of the present application as amended, and in view of the following remarks, is respectfully requested. Applicants note that claims 1, 3-5, 7-10, 12-16, 20, 22-26, 28, 30-38, and 40-47 are currently pending. New claims 46 and 47 have been added. Support for new claims 46 and 47 can be found in the Examples of the original application as filed, e.g., in Examples 1, 4 and 7

A. REJECTION UNDER 35 U.S.C. § 103 OVER WO '781 AND THE MIRANDA PATENT

Claims 1, 3-5, 7-10, 12-16, 20, 22-26, 28, 30-38, and 40-45 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 93/10781 ("WO '781") in view of U.S. 5,091,186 ("the Miranda patent").

This rejection is respectfully traversed. The Examiner acknowledges that WO '186 does not teach the specific delivery profile as recited in the present claims (See, page 4, lines 1-2 of the Office Action).

With respect to the Miranda patent, Applicants respectfully submit that this reference describes transdermal delivery systems in which drug delivery is biphasic. Miranda et al. describe the biphasic delivery as including a delivery phase (e.g., typically of 10 to 14 hours) followed by a secondary phase, (e.g., which virtually no drug is delivered). Miranda et al. describe the total dosing period being about 20 to 28 hours, more preferably about 24 hours, and that the patch may thus be removed and replaced every day at about the same time. See, e.g., column 7, lines 33-40.

It is respectfully submitted that one of ordinary skill in the art would not be motivated to provide a method of treatment comprising applying a transdermal delivery system having mean relative release rates over a 72 hour period as recited in claim 1, or a transdermal delivery system providing mean relative release rates over a 72 hour period

as recited in claim 20, in view of the combination of WO '781 and the Miranda patent, as neither reference describes release rates over a 72 hour period. In fact, the Miranda patent describes a delivery phase of 10 to 14 hours followed by a secondary phase, wherein virtually no drug is delivered.

It is respectfully submitted that one of ordinary skill in the art would not be motivated to maintain the transdermal delivery system described in Miranda et al. in contact with the skin of the patent for at least 3 days as recited in claim 1, as Miranda et al. describe virtually no drug being delivered after the delivery phase of typically 10 to 14 hours. According to Miranda, a new patch must be applied in order to receive additional therapy.

Applicants submit that WO '781 and the Miranda patent do not exemplify felodipine transdermal devices; do not report clinical trials; do not provide any indication that felodipine transdermal systems were ever administered to human subjects; and do not provide any teaching or suggestion of any desired pharmacokinetic parameters for felodipine. Therefore, it is respectfully submitted that these references do not teach or suggest methods of treatment with felodipine devices which provide the several aspects of independent claim 1, including the following:

- maintaining a transdermal delivery system in contact with the skin for at least 3 days;
- maintaining a therapeutic blood level until the end of at least a three-day dosing interval;
- providing a mean relative release rate of from about 2.7 micro grams/cm^2/hr to about 10.8 micrograms/cm^2/hr at 72 hours; and
- providing a plasma level of felodipine of at least 0.1 ng/ml within about 6 hours after application.

Similarly, WO '781 and the Miranda patent, alone or in combination, do not teach several aspects of the present invention as recited in claim 20.

Responsive to the Examiner's comments on page 5, paragraph two ("... the recitation of the [in-vitro permeation test utilizing a Valia-Chien cell] does not impart

patentability ...") it is respectfully submitted that the prior art does not disclose the numeric parameters recited in the presently claimed invention as measured by the Valia-Chien cell. Accordingly, the numeric parameters in relation to the in vitro test do impart a patentable distinction from the prior art.

In the Office Action, the Examiner admits that WO '781 "...does not teach the specific delivery profile claimed by the applicants" and "does not teach the structure of the transdermal delivery system as claimed." However, Applicants respectfully disagree with the Examiner's later position that "[WO '781] is expected to obtain the same delivery profile from the device disclosed by the prior art if it has the same structure and the same amounts of different ingredients such as solvents and permeation enhancers."

Applicants further submit that the Examiner is relying on impermissible hindsight in reconstructing the present invention. The Examiner states that it is "within the skill in the art to select optimal parameters in order to achieve a beneficial effect" and to "manipulate the amount of the drug to obtain the desired delivery profile." However, the Examiner has not provided motivation to one skilled in the art to treat a patient with a device which provides the specific in-vitro release rates and the specific blood plasma level recited in the present claims. Therefore, as the Examiner has not provided motivation to manipulate the prior art in order to arrive at the present claims, Applicants respectfully request that the obviousness rejection over the combination of WO '781 and the Miranda patent be withdrawn.

C. REJECTION UNDER 35 U.S.C. § 103 OVER WO '781, THE MIRANDA PATENT AND THE HILLE PATENT

Claims 37, 38, 44 and 45 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO '781 in view of the Miranda patent, further in view of U.S. Patent No. 5,240,711 ("the Hille patent)."

This rejection is traversed. It is respectfully submitted that Hille et al. does not teach or suggest the in-vitro or in-vivo parameters as recited in the pending claims. Accordingly, this reference fails to cure the deficiencies of the combination of WO '781 in view of Miranda et al. as presented above.

Therefore, Applicant respectfully requests reconsideration and withdrawal of the obviousness rejection over these references.

III. CONCLUSION

Applicants believe that the above-referenced rejections have been obviated and respectfully request that the rejections be withdrawn. Applicants believe that all claims are now in condition for allowance.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance prosecution of the present application. An early and favorable action is earnestly solicited.

Respectfully submitted,
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